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## Cost-Effectiveness of Expanded Newborn Screening in Texas

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### ABSTRACT

**Objective:** Texas House Bill 790 resulted in the expansion of the newborn screening panel from 7 disorders to 27 disorders. Implementation of this change began in 2007. The objective of this study was to estimate the incremental cost-effectiveness of the expanded newborn screening program compared with the previous standard screening in Texas. **Methods:** A Markov model (for a hypothetical cohort of Texas births in 2007) was constructed to compare lifetime costs and quality-adjusted life-years (QALYs) between the expanded newborn screening and pre-expansion newborn screening. Estimates of costs, probabilities of sequelae, and utilities for disorder categories were obtained from a combination of Texas statistics, the literature, and expert opinion. A baseline discount rate of 3% was used for both costs and QALYs, with a range of 0% to 5%. Analyses were conducted from a payer's perspective, and so only direct medical cost estimates were included. **Results:** The

lifetime incremental cost-effectiveness ratio for expanded versus pre-expansion screening was about \$11,560 per QALY. The results remained robust to both deterministic and probabilistic sensitivity analyses. **Conclusions:** Expanded newborn screening does result in additional expenses to the payer, but it also improves patient outcomes by preventing avoidable morbidity and mortality. The screened population benefits from greater QALYs as compared with the unscreened population. Overall, expanded newborn screening in Texas was estimated to be a cost-effective option as compared with unexpanded newborn screening.

**Keywords:** children, cost-effectiveness analysis, health economics methods, model, quality-adjusted life-years.

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### Background

Newborn screening involves laboratory analysis of blood samples from newborns to detect inborn errors of metabolism and allows timely diagnosis of serious and life-threatening conditions. Screening should be conducted in the first week of a baby's life to ensure treatment initiation before the age of 4 weeks. Timely treatment helps prevent irreversible mental retardation, physical disability, and death in most cases [1]. Newborn screening started in the United States in early 1960s when Dr. Robert Guthrie developed a bacterial inhibition assay for identifying infants with phenylketonuria (PKU). His technique of collecting blood samples on filter paper made it possible to implement PKU screening at the population level [2]. Gradually, more disorders were added to the newborn screening panel.

The use of tandem mass spectrometry (MS/MS) has made it possible to screen for as many as 50 disorders by using the same blood specimen. With the ability to screen for more disorders, most US states expanded their newborn screening panel although the expansion process varied greatly across states. The economic viability of these expansions has been studied by many researchers. In 2002, Schoen and Baker [3] reported that screening for multiple disorders with MS/MS yields an incremental cost-effectiveness ratio (ICER) of \$5827 per quality-adjusted life-year (QALY). Of the newly added conditions, medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is the most common, affecting about 1 in

20,000 of all newborns in the country. A few studies have been based on the cost-effectiveness of this condition alone. Insinga et al. [4], Venditti et al. [5], and Tran et al. [6] reported that universal screening for MCADD by using MS/MS is a cost-effective option. Two studies based in California focused on MCADD and several other conditions and reported that MS/MS screening is a cost-effective strategy for most conditions, except congenital adrenal hyperplasia or galactosemia [7,8]. A Canadian study assessed the expansion of the existing screening system in Ontario and concluded that the average cost of screening for PKU plus 14 other disorders is Can \$95,000 per life-year gained [9]. It is important to note that in each of the studies, comparisons may differ. Reasons for this include differences in the base case, patient population, and number of disorders already being screened, and measures of cost-effectiveness used. Such differences will automatically impact the results of an economic analysis that is always relative to the baseline comparator.

The newborn screening panel in Texas was expanded when House Bill 790 mandated that the state should offer screening for at least 28 conditions recommended by the American College of Medical Genetics [10]. In 2007, Texas began to screen for 27 of the 29 recommended conditions. This was a large increase from the 7 disorders that were included in the panel prior to this expansion. Texas performs two screens on newborns by using separate blood samples obtained at the ages of 24 to 48 hours and 7 to 14 days, respectively. Blood samples from infants who test positive after the second screen need to be sent for confirmatory testing.

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† This study was completed while the author was at the University of Texas at Austin.

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## Objective

The main objective of this study was to report the incidence of various newborn screening disorders for the 2007 birth cohort in Texas and to estimate the cost-effectiveness of the expanded newborn screening by using Texas-specific data.

## Methods

### Overview

We developed a cost-effectiveness Markov model by using Tree-Age to represent the screening outcomes and the sequelae encountered by children who are diagnosed with one of the metabolic disorders that are included in the expanded newborn screening panel of Texas. Because of lack of sufficient information on incidence and sequelae, we could include only the following disorders in our analysis: arginosuccinic acidemia (ASA), citrullinemia (CIT), homocystinuria (HCY), maple syrup urine disease, MCADD, glutaric acidemia type I (GA-I), and classical organic acid disorders (COAD) (including methylmalonic acidemia, propionic acidemia, and isovaleric acidemia). One or more disorders were grouped together if they shared physiological similarities. The model included a hypothetical cohort of infants born in Texas in 2007, since newborn screening was expanded in January of that year. We adopted the perspective of the payers in Texas and discounted the costs and QALYs at a base rate of 3%.

### Model assumptions

The following assumptions were used while conducting the cost-effectiveness analysis:

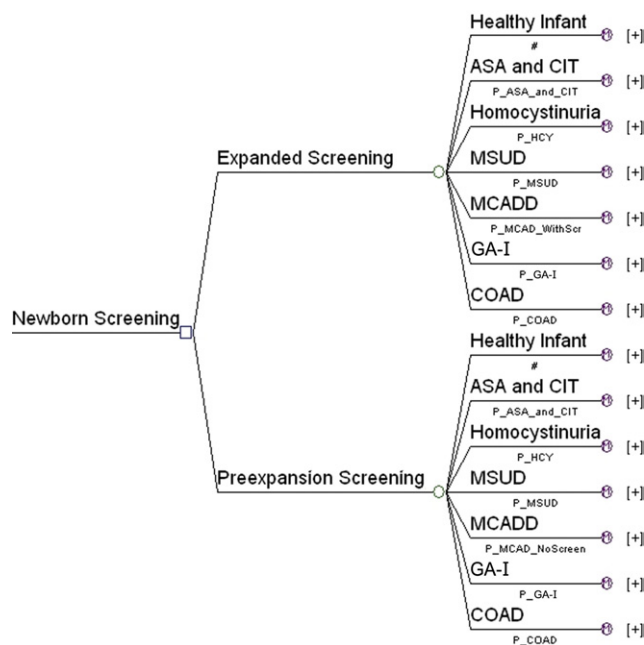
1. A child can have only one metabolic disorder.
2. Testing is timely (specimens obtained within 24–48 hours for first screen and within 7–14 days for second screen), and testing methods are appropriate (i.e., with high sensitivity and specificity).
3. MS/MS is used for screening for the disorders included in this study.
4. In an individual experiencing more than one sequela, disutility caused by the most debilitating sequela also includes the disutility caused by other, less debilitating comorbidities.
5. Newborn screening in Texas is universal.

### Cycle length, termination condition, and discounting

Each cycle length was 1 year. Half-cycle corrections were used for initial values of recurring costs such as the costs of special diet and medications. One-time costs incurred in the first year of life, such as the costs of screening and diagnostic testing, however, were not subject to half-cycle correction. A discount rate of 3% was used, and all costs were adjusted to 2007 USD. The Markov model was terminated when 99.99% of the cohort had entered the “dead” state.

### Model structure

As shown in Figure 1, the model structure included two main branches, one each for the expanded and the unexpanded screening programs. Subbranches representing six disorder categories (based on common physiological characteristics) and the healthy state were used to compare the two scenarios. An infant could either be affected with one of the screened disorders or be healthy. A large majority of healthy infants should have a negative screen result, while some may have a false-positive screen result (positive screen results that come out negative after confirmatory testing). Because the sensitivity of screening via MS/MS is close to 1.0, we chose not to include a branch for false-negative results. Figure 2 shows an example of a disease-specific subtree for HCY. HCY is



**Fig. 1 – ASA, arginosuccinic acidemia; CIT, citrullinemia; COAD, classical organic acid disorders; GA-1, glutaric acidemia type I; HCY, homocystinuria; MCADD, medium chain acyl-CoA dehydrogenase deficiency; MSUD, maple syrup urine disease; P\_disorder name, probability of disorder.**

an enzyme deficiency disorder that may be grouped with other urea cycle disorders. Because of some unique sequelae of this disorder, it was analyzed as a separate condition. Accumulation of homocystine may cause mental retardation, lens abnormalities, and skeletal abnormalities. Lens abnormalities can be corrected, and so occur in only one cycle of the structure. Premature death may occur because of thromboembolism (blood clot formation). Treatment for HCY includes restricted diet and B<sub>6</sub>, B<sub>12</sub>, and betaine supplementation. In addition, treatment may include cystine in some cases.

### Markov states

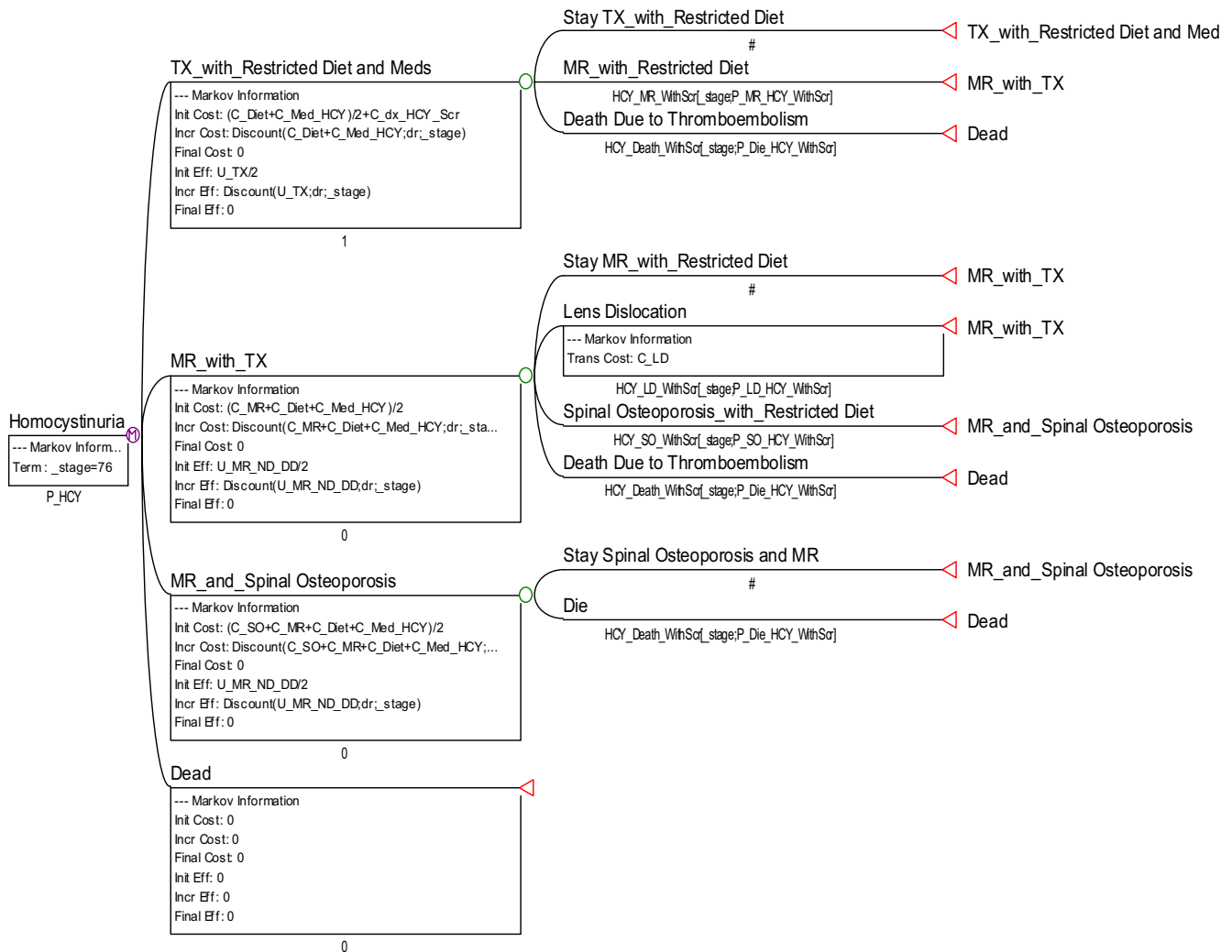
A healthy infant could either test negative (which is true in most cases) or test false positive. In the event of a false-positive screen, the infant would have to undergo confirmatory testing. The model accounts for the cost and disutility associated with a false-positive screen in the first year of life. Once it is confirmed that the infant does not have the suspected disorder, there is no more costs or disutility allocated to a false-positive case.

True-positive cases would incur the cost and disutility associated with confirmatory testing in the first year of life, as well as treatment costs and loss of quality of life because of their condition for the rest of their lives.

All individuals in the hypothetical cohort were exposed to the risk of “all-cause mortality,” which estimates the average risk of death, based on age and sex, by using US Census estimates. Those with one of the conditions included in the newborn screening panel had an additional risk of dying from their disease. This approach was used to ensure a more realistic estimate of the effect of screening.

### Event probabilities

The probability of testing positive for any one of the disorders was equal to the prevalence of that particular disorder. The model structure for the unexpanded screening was very similar to that for



**Fig. 2 – HCY, homocystinuria; MR, mental retardation; TX, treatment; P\_HCY, probability of HCY; C\_diet, cost of special diet; C\_Med, cost of medication; dr, discount rate; U\_TX, utility of being on treatment; Init cost, initial cost; Incr cost, incremental cost; Eff, effectiveness; WithScr, with screening; LD, lens dislocation; SO, spinal osteoporosis; MR, mental retardation; ND, neurological damage; DD, developmental delay.**

expanded screening. In the absence of screening, however, patients would be diagnosed via clinical symptoms. Table 1 shows the actual incidence data for 2007 obtained from the Texas Department of State Health Services. Estimates from the literature and expert opinion were used to reflect different event probabilities in screened and unscreened patients (where in the absence of screening, the infant may experience delayed diagnosis and a higher probability of morbidity and mortality). While it may be argued that screening can increase the possibility of diagnosis, especially among those with milder forms of a condition, there is insufficient data to allocate different prevalence to the screened versus unscreened populations of the same condition. The only exception is MCADD where on the basis of recently published evidence, we were able to allocate different probability of testing positive to screened and unscreened cohorts. The estimated probabilities of various events associated with both the expanded and unexpanded branches are listed in Table 2.

### Costs

The study included all direct medical costs incurred during the screening and treatment of cases. Specific categories include cost

of screening, cost of confirmatory testing, cost of false-positive result, cost of disease management (e.g., special diet, medications, emergency room visits, and inpatient stay), and cost of specific sequelae (e.g., mental retardation, neurological damage, developmental delay, lens dislocation, spinal osteoporosis, chronic renal failure, and liver damage). The total cost of screening includes the cost of the first and second screens and the cost of confirmatory testing. The total fee charged by the Texas Department of State Health Services for the first and second screens was used as a proxy for the cost of screening. The fees charged by the Baylor Metabolic Institute for confirmatory testing were used as a proxy for the cost of confirmatory testing. Detailed estimates of costs of confirmatory testing are shown in Table 3. Although this study specifically addressed the perspective of third-party payers in Texas, in the absence of Texas-specific costs, US national averages were used for estimating the costs of various sequelae. All costs were adjusted to reflect values in 2007 USD by using the medical care component of the consumer price index ([http://www.bls.gov/cpi/cpi\\_dr.htm#2007](http://www.bls.gov/cpi/cpi_dr.htm#2007); accessed May 13, 2010). Detailed estimates of cost inputs used in the model are presented in Table 4.

**Table 1 – Incidence of various disorders (detected via MS/MS) in Texas in 2007.**

Disorder	Expected incidence for 400,000 births	Total cases in 2007	Females (n)	Males (n)	White (n)	Hispanic (n)	Asian (n)	African American (n)
ASA and CIT	5	3	2	1	1	1	1	0
Homocystinuria	2	3	2	1	0	3	0	0
MSUD	2	1	1	0	0	1	0	0
MCADD and other fatty acid disorders (VLCAD and LCHAD)	27	30	13	17	19	9	0	2
GA-1	13	7	4	3	3	3	0	1
MMA, PA, IVA (COAD)	3	4	3	1	3	1	0	0
Total	56	48	25	23	26	18	1	3

ASA, arginosuccinic acidemia; CIT, citrullinemia; COAD, classical organic acid disorders; GA-1, glutaric acidemia type I; IVA, isovaleric acidemia; LCHAD, long-chain hydroxyacyl-CoA dehydrogenase deficiency; MCADD, medium chain acyl-CoA dehydrogenase deficiency; MMA, methylmalonic acidemia; MS/MS, tandem mass spectrometry; MSUD, maple syrup urine disease; PA, propionic acidemia; VLCAD, very-long-chain acyl-CoA dehydrogenase deficiency.

### Quality-of-life estimates

Various aspects of screening and disease management can lead to short- and long-term loss in quality of life. We included utility estimates for false-positive screen results, dietary treatment, and disease-related sequelae (e.g., mental retardation, neurological damage, developmental delay, liver disease, chronic renal failure, and spinal osteoporosis). These estimates were obtained from the literature. Detailed estimates of quality-of-life inputs used in the model are presented in Table 5.

### Results

Table 6 shows the lifetime estimates of cost and effectiveness (with and without screening) for each expanded disorder category. For HCY, screening was the dominant strategy compared with not screening. For ASA and CIT, screening resulted in an estimated ICER of about \$10,000 per QALY, which is higher than that for other disorders included in the analysis. For all the other disorder categories, screening resulted in an ICER of approximately \$4000 or

**Table 2 – Probability of events.**

	Variable	With screening (range)	Without screening (range)	Reference
ASA and CIT	Incidence in Texas (2007)	1 in 130,000	1 in 130,000	DSHS
	Probability of mental retardation	0.20 (0.16–0.24)	0.20 (0.16–0.24)	[11]
	Probability of death	0.60 (0.48–0.73)	0.80 (0.64–0.97)	[11]
HCY	Incidence in Texas (2007)	1 in 130,000	1 in 130,000	DSHS
	Probability of lens dislocation	0.05 (0–0.10)	0.70 (0.57–0.85)	[11–13]
	Probability of mental retardation	0.09 (0–0.18)	0.89 (0.79–0.99)	[11–13]
	Probability of spinal osteoporosis	0.05 (0–0.10)	0.50 (0.35–0.67)	[11–13]
	Probability of death	0.10 (0–0.20)	0.14 (0.04–0.24)	[11–13]
MSUD	Incidence in Texas (2007)	1 in 400,000	1 in 400,000	DSHS
	Probability of developmental delay	0.022 (0.018–0.026)	0.06 (0.045–0.075)	[14]
	Probability of neurological damage	0.1 (0.075–0.125)	0.1 (0.075–0.125)	[14]
MCADD	Probability of death	0.06 (0.045–0.075)	0.90 (0.80–1.0)	[14]
	Incidence in Texas (2007)	1 in 25,000	1 in 10,000	DSHS, [15]
	Probability of developmental delay	0.04 (0.03–0.06)	0.08 (0.06–0.10)	[16]
GA-I	Probability of death	0.042 (0.037–0.045)	0.25 (0.225–0.275)	[16]
	Incidence in Texas (2007)	1 in 57,000	1 in 57,000	DSHS
	Probability of neurological damage	0.35 (0.32–0.39)	0.90 (0.72–0.99)	[11,17,18]
COAD	Probability of death	0.05 (0.045–0.056)	0.32 (0.29–0.35)	[11,17,18]
	Incidence in Texas (2007)	1 in 100,000		DSHS
	Probability of neurological damage	0.27 (0.25–0.30)	0.73 (0.66–0.81)	[11,19]
	Probability of chronic renal failure	0.05 (0.045–0.055)	0.41 (0.37–0.45)	[11,19]
Screening	Probability of death	0.11 (0.10–0.12)	0.50 (0.45–0.55)	[11,19]
	Probability of false positive	0.020 (0.018–0.022)	0.0175 (0.010–0.019)	DSHS

ASA, arginosuccinic acidemia; CIT, citrullinemia; COAD, classical organic acid disorders; DSHS, Department of State Health Services; GA-1, glutaric acidemia type I; HCY, homocystinuria; MCADD, medium chain acyl-CoA dehydrogenase deficiency; MSUD, maple syrup urine disease.



**Table 3 – Cost of screening and confirmatory testing in Texas for 2007\*.**

Disorder name	Confirmatory test(s)	Current procedural terminology code	Estimated cost (\$)	Total cost of confirmatory testing per case (\$)	False-positive cases in 2007	Estimated cost of confirmatory testing for false-positive cases (\$)
Arginosuccinic aciduria/citrullinemia	Plasma amino acids	82139	140	370	45	16,650
	Supplemental newborn screening	83788	35			
Homocystinurea	Urine organic acids	83918	195	220	205	45,100
	Homocystine total	83090	45			
	Plasma amino acids	82139	140			
	Supplemental newborn screening	83788	35			
Maple syrup urine disease	Plasma amino acids	82139	140	370	79	29,230
	Supplemental newborn screening	83788	35			
MCADD and other fatty acid disorders	Urine organic acids	83918	195	400 <sup>†</sup>	474	189,600
	Acylcarnitine profile	82017	110			
	Carnitine levels	82379	80			
	MCADD DNA analysis	83890	150			
	MCADD unknown mutation	83890	2000			
	MCADD panel of 8 mutations	83890	850			
	Mitochondrial beta oxidation	88233	750			
	Supplemental newborn screening	83788	35			
Glutaric acidemia type I	Urine organic acids	83918	195	340	93	31,620
	Acylcarnitine profile	82017	110			
	Supplemental newborn screening	83788	35			
Isovaleric acidemia	Urine organic acids	83918	195	340	170	57,800
	Acylcarnitine profile	82017	110			
	Supplemental newborn screening	83788	35			
Methylmalonic acidemia/propionic acidemia	Urine organic acids	83918	195	420	42	17,640
	Acylcarnitine profile	82017	110			
	Carnitine levels	82379	80			
	Supplemental newborn screening	83788	35			
	Urine organic acids	83918	195			

Source. Institute of Metabolic Disease at Baylor Research Institute (<http://www.baylorhealth.edu/imd/disease.htm>).

MCADD, medium chain acyl-CoA dehydrogenase deficiency.

\* Texas screens all newborns twice. The total cost of screening was \$39 before the expansion and \$59 after the expansion.

<sup>†</sup> Assuming most cases of MCADD would need basic confirmatory testing and not the more extensive DNA or mutation analysis.

less per QALY. The overall ICER for expanded versus preexpansion screening was about \$11,560 per QALY at the base discount rate of 3% (Table 7).

The tornado diagram in Figure 3 shows the impact of the most influential variables on the results of the cost-effectiveness analysis. The utility of being on treatment without additional complications was the most influential variable, followed by yearly cost of carnitine supplementation. Among other important variables were probability of death due to ASA and CIT, with and without screening; cost of false-positive screen; and cost of special diet.

### Results of probabilistic sensitivity analysis

Figure 4 shows the cost-effectiveness scatter plot obtained with a probabilistic sensitivity analysis using a discount rate of 3% for costs and QALYs. The mean cost for expanded screening was \$115.79 (SD = \$2.0; range = \$108.96–\$122.99). Mean effectiveness for expanded screening was 29.921 QALYs (SD = 0.0008 QALYs;

range = 29.9195–29.9241 QALYs). For preexpansion screening, mean cost was \$83.10 (SD = \$1.68; range = \$77.09–\$89.43) and mean effectiveness was 29.9190 QALYs (SD = 0.00611 QALYs; range = 29.9172–29.9208 QALYs). Most of the data points (97.5%) for expanded screening were at or below a cost of \$119.74 and below an effectiveness of 29.9233 QALYs. For preexpansion screening, 97.5% of the data points were at or below a cost of \$86.39 and below an effectiveness of 29.92083 QALYs.

### Discussion

As shown by the results of this analysis, expanded screening may cost an additional \$11,560 per QALY at the base discount rate of 3%. Although the absolute difference in the effectiveness of the two strategies at a population level is relatively small, at 0.002829 QALYs, it can potentially make a significant difference for the infants detected with one of the disorders. For most of the disorders,

**Table 4 – Treatment costs (in 2007 USD).**

Variable description	Estimated average cost (\$)	Lower estimate of cost (\$)	Higher estimate of cost (\$)	Reference
Yearly cost of carnitine supplements for MCADD	6,600	6,000	7,200	[9]
Yearly cost of chronic renal failure	9023	7,735	9,797	[20], estimate
Yearly cost of developmental delay	5,670	5,300	6,400	[21]
Yearly cost of special diet for metabolic disorders	4,360	4,000	4,800	[9]
Yearly cost of emergency room visits for MCADD patients*	500	400	600	[4,5,21–23,32]
Yearly cost of inpatient stay for MCADD patients*	2,500	2,000	3,000	[4,5,21–23,32]
One-time cost of lens dislocation	3,085	2,683	3,353	[24]
Yearly cost of ASA and CIT medications	35,780	32,000	40,000	[9]
Yearly cost of medications for homocystinuria	5,000	4,000	6,000	[9]
Yearly cost of COAD medications	1,500	1,200	1,800	[9]
Yearly cost of mental retardation	5,635	4,025	6,708	[25]
Yearly cost of neurological disorders	3,891	2,683	5,098	[25]
Yearly cost of spinal osteoporosis	434.00	325.00	542.00	[26]
One-time average cost of resolving a false-positive screen, inclusive of repeat screens, confirmatory testing, and other expenses	1,000	800	1,200	Expert opinion, estimate

ASA, arginosuccinic acidemia; CIT, citrullinemia; COAD, classical organic acid disorders; MCADD, medium chain acyl-CoA dehydrogenase deficiency.

\* We used frequency of emergency room visits and hospitalizations from Australian studies and then multiplied those with US cost estimates.

expanded screening is associated with more costs coupled with greater quality of life.

For ASA and CIT, screening costs an estimated additional \$10,000 per QALY at the base rate of 3%, which is likely due to the higher cost of treatment for these disorders. Although screening results in higher survival among patients with ASA and CIT, rates of mental retardation tend to remain high among the survivors, resulting in poor quality of life for survivors. For HCY, screening not only costs less due to lower treatment costs but also results in greater quality of life due to the reduced likelihood of adverse outcomes in the screened group. A vast majority of the unscreened patients are at the risk of lens dislocation and chronic skeletal abnormalities as they grow older, leading to significant direct medical costs and reduced quality of life. In contrast, only a few of the screened patients run the risk of lens dislocation or spinal osteoporosis. Therefore, screening is the *dominant* strategy for HCY. For maple syrup urine disease, there is a stark contrast in the QALYs for screened versus unscreened patients. This can be explained by the extremely high mortality (which translates to zero QALYs) in the first two years of life for children who may be diagnosed late. Screening for GA-I also results in a substantial increase in QALYs, while still remaining cost-effective. The ICER of screening and treatment for MCADD is about \$633 per QALY, which is lower than some of the published estimates [4]. Possible reasons for this difference could be the use of different model inputs. Furthermore, the treatment plan for cases of MCADD diag-

nosed via screening or clinical symptoms would be very similar, yet QALY improvement in screened cases is significant due to the reduced risk of mortality. Screening for COAD is also cost-effective, with the ICER for screened group at about \$1800 per QALY. Timely intervention is crucial in this group of disorders, and patients can potentially have a better quality of life without incurring extremely high treatment costs.

Results of the one-way sensitivity analyses point to several variables that may impact the results of the cost-effectiveness analysis. Study results were sensitive to variations in discount rate because it impacts all the costs and utilities after the first year of life. Within the cost category, cost of false positives and cost associated with special diet were the most influential variables. If the cost of ruling out false-positive screens is very high, it can potentially impact the cost-effectiveness of the program. The cost of special diet impacts every child who tests positive for any of the disorders and is placed on a special diet. The cost of carnitine supplementation is also an important variable in the cost category. Although there is no evidence-based recommendation for carnitine supplementation in patients with MCADD, according to expert opinion, carnitine supplementation is frequently recommended, especially in the United States (this practice may not be followed in European countries) [30,31]. In our model, we included the cost of carnitine supplementation for patients with complications related to MCADD [30,31]. Because MCADD is the most prevalent condition included here, cost of carnitine can affect a signif-

**Table 5 – Utility estimates.**

Variable name	Description	Estimated average utility	Range	Reference
U_CRF	Utility of having chronic renal failure	0.67	0.58–0.74	[19]
U_FP	Utility of receiving a false-positive screen result	0.97	0.95–0.99	[5]
U_LT	Utility of liver transplant	0.67	0.58–0.74	[27]
U_MR	Utility of mental retardation	0.79	0.59–0.84	[28]
U_DD	Utility of developmental delay	0.843	0.792–0.881	[29]
U_ND	Utility of neurological damage	0.84	0.70–0.85	[28]
U_SLD	Utility of severe liver disease	0.20	0.10–0.3	[27]
U_SO	Utility of spinal osteoporosis	0.92	0.88–0.94	[24]
U_TX	Utility of being on treatment without complications	0.90	0.85–0.95	[5]

**Table 6 – Average cost and effectiveness by disorder at 3%.**

	With screening		Without screening		ICER (\$/QALY)
	Cost (\$)	Effectiveness	Cost (\$)	Effectiveness	
ASA_CIT	681,455.00	14.34	538,334.00	11.3	9,969.24
HCY	267,699.00	24.09	333,594.00	21.04	Dominant
MSUD	136,607.00	25.03	36,303.00	5.94	4,001.41
MCADD	266,711.00	24.56	250,678.00	19.84	632.97
GA-I	291,269.00	24.73	217,145.00	19.91	2,977.42
COAD	184,436.00	23.46	142,468.00	15.02	1,773.90

ASA, arginosuccinic acidemia; CIT, citrullinemia; COAD, classical organic acid disorders; GA-1, glutaric acidemia type I; HCY, homocystinuria; ICER, incremental cost-effectiveness ratio; MCADD, medium chain acyl-CoA dehydrogenase deficiency; MSUD, maple syrup urine disease; QALYs, quality-adjusted life-years.

icant number of patients each year. Within the probability category, a significant decline in the probability of death due to some disorders is seen for the screened versus unscreened populations. A decline in mortality is the only major difference between the screened and unscreened patients when other sequelae do not differ much despite screening. This may explain the influence of probability of death for ASA and CIT as an influential variable in this category. The probability of neurological damage also differs significantly for the screened versus unscreened populations of patients with GA-I and patients with COAD. So, these variables also impact the overall study results. For the categories of utility values used in the Markov model, the utility of being on treatment (with special diet) without any additional complications impacts most of the members of the cohort. Consequently, this variable is influential as shown by the tornado diagram.

Results of the overall cost-effectiveness analysis are somewhat comparable with the results of other studies done in the past. Other studies may differ in terms of the comparators included, perspective of analysis, costing year, and country. For example, the base-case results of the current study show that the ICER for expanded screening was approximately \$11,560 per QALY at a discount rate of 3%. In their 2002 study, Schoen and Baker [3] reported their base-case estimate as \$5827 per QALY. Their results were based on estimates of a number of disease states, including PKU. While the current study includes cost-effectiveness estimates of screening for most of the disorder categories used by Schoen and Baker, it does not include cost and effectiveness analyses for PKU. Inclusion of PKU may have changed the results of the study because it is a much more prevalent condition as compared with many other disorders. Similarly, the current study differs from the analysis by Carroll and Downs [7] in terms of the disorders included and the utility estimates for sequelae. The current study results of \$11,560 per QALY are also higher than the cost-effectiveness estimate provided by Feuchtbaum and Cunningham [8]. According to their estimates, screening cost \$1628 per QALY in the base-case estimate. Instead of allocating separate costs to each of the disease sequelae, they had used an average estimate of \$1 million for the cost of lifetime treatment and follow-up. Their estimate was derived from a research article based on a Centers for

Disease Control and Prevention report published in 2003 [25]. The source article, however, elaborates that most of the costs in this \$1-million estimate are based on the productivity loss due to lost wages and early mortality. The current study does not include productivity losses incurred either by the parents or by the patients (after they reach adulthood), which may be different than some other studies conducted in the United States. If indirect costs were included in the present study, the results may be more comparable to the conclusions of Feuchtbaum and Cunningham. Study results also share some similarities with those of a more recent study based on the cost-effectiveness of expanding newborn screening in Ontario, Canada [9]. In their study, Cipriano et al. [9] reported that if MS/MS is used for screening newborns for PKU along with other metabolic disorders, it would only be cost-effective to include PKU and 14 other conditions on a combined newborn screening panel. The inclusion of maple syrup urine disease, GA-I, COAD, and MCADD and other fatty acid disorders along with PKU would be cost-effective at less than C\$70,000 per life-year gained. Results of the current study also suggest that screening for these conditions is cost-effective. There are some key differences, however, between the current study and the Cipriano study, such as the use of life-years versus quality-adjusted life-years. Furthermore, the Cipriano study was proposing the expansion of newborn screening in Ontario. Therefore, they included the disorders in a stepwise manner where the decision to include each successive disorder in the panel could be based on incidence, prevalence, and the availability of effective treatment. While these are valid points to consider before any expansion of an existing program, they may not be useful for estimating the cost-effectiveness of an expansion that has already taken place (such as in the case of Texas), where it may be more relevant to consider simultaneous inclusion of a number of disorders.

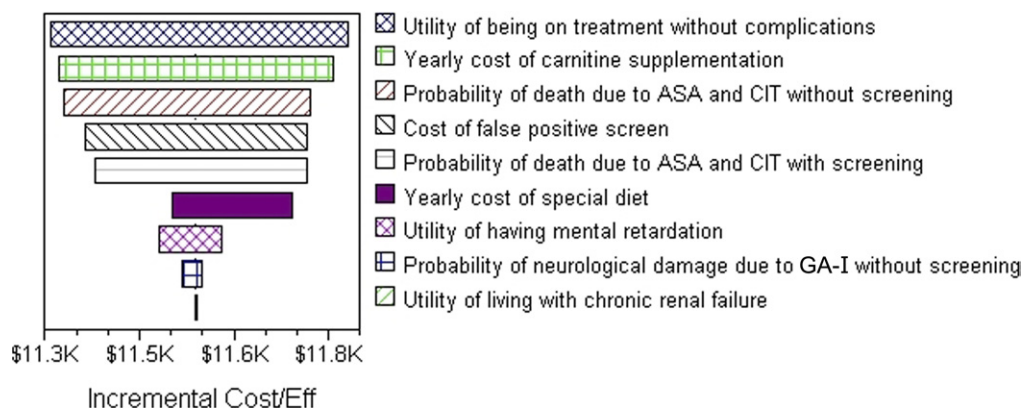
### Study limitations

One of the main limitations of this study is that estimates from the literature and experts were used instead of actual patient data for most of the costs, probabilities, and outcomes. Each of the published studies has its own inherent limitations, and the screening program described in a study may be systematically different from

**Table 7 – Results of overall cost-effectiveness analysis at 3%.**

Strategy	Cost (\$)	Incremental cost (\$)	Effectiveness	Incremental effectiveness	C/E	Incremental C/E (ICER)
Preexpansion screening	83.08897		29.91901		2.77713	
Expanded screening	115.7953	32.70637	29.92184	0.002829	3.869928	\$11,559.86per QALY

C, cost; E, effectiveness; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.



**Fig. 3 – Tornado diagram at expanded screening vs preexpansion screening. ASA, arginosuccinic acidemia; CIT, citrullinemia; GA-I, glutaric acidemia type I.**

the newborn screening program of Texas. Many of the published results are also based on relatively short-term follow-up. For example, the hospitalization data for patients with MCADD in Australia were reported for only the first four years of life [22]. We estimated the likelihood of hospitalization for children older than 4 years. Furthermore, some of the studies have been conducted in specialty clinics or in high-incidence communities. Results from such studies may not be generalizable to other health care facilities or to communities where many of the disorders are extremely rare. Expert opinion was used for some of the sequelae, where data from the literature were unclear or insufficient, which may cause some subjectivity. There is also very little information available on the quality-of-life issues related to dietary treatments.

The current analysis included only a subset of the conditions that are screened for under the expanded panel. Inclusion of all the disorders was not feasible because of a lack of sufficient information on sequelae and other model parameters. Specimens for screening may be drawn from infants between 24 and 72 hours of birth, and results are usually available 5 to 10 days from birth. Some infants may die before any concrete diagnosis can be made.

It is important to recognize that because of screening, milder cases of the disease may also be detected. Outcomes for these patients will be inherently better than for those who have the severe form of the same disorder. Inclusion of mildly affected patients in the cohort may create a positive bias in favor of screening. On the other hand, when data on unscreened cohorts are used, they include only the more severe cases because the mild forms of the disease may go undiagnosed. Their disease prognosis is worse

because of the severity of their disease, which confounds the effect of late treatment (as compared with that of screened cohorts who are likely to receive early treatment).

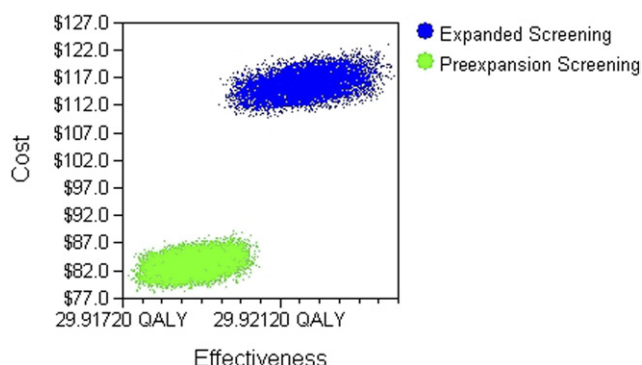
The model included the fee charged for screening as a proxy for the cost of screening. Because of lack of sufficient information, screening costs were considered as a single estimate and were not apportioned among various disorders. The cost of confirmatory testing may differ depending on individual laboratory practices and pricing. Estimates used in this study were obtained directly from the laboratory that supports the screening program in Texas. Another limitation was the lack of utility estimates specific to newborn screening disorders. Although there is literature on conditions such as mental retardation, neurological damage, and renal failure, it is problematic to account for the disutility caused by individual sequelae when a patient is experiencing more than one complication. There have been comparisons of the disutility caused by a false-positive newborn screen result with that of a false-positive cancer screen. It may be argued that the disutility of a false-positive cancer screen often pertains to the patient (except in pediatric patients), whereas most of the emotional trauma of a false-positive newborn screen is experienced by the infant's family. Last, utility estimates of being on special diet are also poorly understood.

### Significance of this study

Since the expansion of Texas's screening panel in 2007, this is the first study to estimate the cost-effectiveness of the newborn screening program in Texas. Results of the present study capture a variety of aspects in addition to treatment costs, such as cost estimates for laboratory activities (screening and confirmatory testing) and case management activities. The study methodology provides a compilation of disease prognosis and outcomes data (based on severity) obtained from a number of recent studies. Study results may further substantiate the policy decision of expanding newborn screening in Texas, particularly the long-term disease management aspect of newborn screening. Estimates of long-term costs, such as cost of special diet, and QALYs may be useful in future plans regarding patient care and coverage of treatment expenses.

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**Fig. 4 – CE scatter plot. C, cost; E, effectiveness; QALY, quality-adjusted life-year.**



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